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(54) Title: USE OF RETINOID GLYCOSIDES IN TOPICAL PHARMACEUTICAL COMPOSITIONS			
(57) Abstract			
<p>Certain stable analogues of retinoic acid are found to be useful in the treatment of dry eye and related ailments, and skin disorders such as acne, psoriasis, skin aging and wound healing. These compounds are much more soluble than retinoic acid, and may therefore be formulated in standard.</p>			

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· USE OF RETINOID GLYCOSIDES IN TOPICAL PHARMACEUTICAL COMPOSITIONS

5 · BACKGROUND OF THE INVENTION· 1. Field of the Invention

The present invention relates to the use of certain retinoic acid analogues as therapeutic agents, particularly as wound healing agents, in irrigating solutions, and for the treatment of skin disorders and dry eye syndromes. As used herein, the term "dry eye syndromes" includes but is not limited to: ocular cicatricial pemphigoid, Stevens-Johnson Syndrome, xerophthalmia, hypovitaminosis A, trachoma, and trauma to the conjunctiva. The retinoic acid analogues of the present invention include retinoyl β -glucuronide and retinoyl β -glucose and their oxidative degradation products. The present invention also relates to topical pharmaceutical compositions comprising such compounds as well as methods for their use.

20 · 2. Discussion of Related Art

Dry eye symptoms and related eye ailments, including more transitory discomfort, are among the most commonly reported medical complaints. These ailments are well known in the scientific and patent literature. The following patents are incorporated by reference herein to the extent that they provide additional background on the ailments and 25 recognized indications for their relief: US 4,039,662; US 3,981,133; US 3,920,810; US 3,843,782; US 4,131,651; US 4,826,871; and Belgian Patent 844,544. A further description of the physical manifestations associated with dry eye disorders is seen in a scientific paper presented by Scheffer Chuei-Goong Tseng at the Science Writers Seminar in Ophthalmology, sponsored by Research to Prevent Blindness, Inc., held in Washington 30 DC from September 30 to October 3, 1984: Tseng, "Topical Vitamin A Treatment for Dry Eye Disorders," pages 1-6 (1984). The Tseng article describes experiments in which

an ointment containing Vitamin A is utilized to treat dry eye disorders associated with Sjogren's Syndrome and Stevens-Johnson Syndrome.

The tear film is thought to be composed of three layers: an outer, lipid layer secreted by the meibomian glands; a middle, aqueous layer secreted by the main and accessory lacrimal glands; and an inner, mucin layer which is in direct contact with the conjunctival and corneal epithelium and which is secreted by the conjunctival goblet cells. The functions of tears and the corneal epithelium are three-fold: to form a smooth refractive corneal surface; to form a barrier between the environment and the stroma; and to provide a wettable, lubricated surface to allow comfortable blinking. The microvilli on the surfaces of the most superficial epithelial cells are covered with a glycocalyx that interacts with the mucin layer of the tear film.

Deficient functioning of the different layers of tear film may cause different symptoms of dry eye syndromes. For example, cicatricial pemphigoid and Stevens-Johnson Syndrome are two disorders usually described as mucin deficiency dry eye syndromes. A classic example of mucin deficiency caused by degeneration or loss of goblet cells is hypo-vitaminosis A. This can be induced experimentally in laboratory animals and is found endemically in developing countries.

It appears that Vitamin A is necessary for maturation of goblet cells, and that it also plays an essential role in the biosynthesis of cell surface glycoconjugates. In fact, it appears that Vitamin A is required for the normal synthesis of cell surface glycoconjugates in the corneal epithelium. Non-wetting of the ocular surface, one of the signs of Vitamin A deficiency, is generally attributable to the loss of mucous glycoproteins. Although Applicants do not wish to be bound to any particular theory, the most likely mechanism for the delivery of retinol to the cornea is by uptake from circulation and/or from tears. Given the importance of Vitamin A to the ocular surface, its secretion by the lacrimal gland into tear fluid has obvious physiological implications in the maturation and maintenance of normal goblet cell function. Within the cell, Vitamin A is bound to retinol binding protein (RBP). The binding of retinol to cellular RBP is greatly impaired in

corneas of Vitamin A-deficient rabbits. See, for example, Berman, E., Biochemistry of the Eye, Plenum Press: NY; 1991, pp. 93-95. Vitamin A is an essential component in the chemical process of vision. Among the major function of retinol in corneal epithelium, two functions have been clearly established: control of keratitis expression; and synthesis of glycoconjugates.

Retinoic acid (the acid form of Vitamin A) is also effective in treating disorders of the eye. This may be by enhancing the healing rate of experimentally-induced corneal epithelial wounds and speeding corneal healing when topically applied to xerophthalmic patients; however, both retinoic acid and Vitamin A are very insoluble in water, and both are highly susceptible to oxidation in the presence of oxygen or in air. These compounds have therefore been primarily formulated in petroleum-based ointments.

Ointments are greasy, inconvenient, and often interfere with vision; therefore, several attempts have been made in the past to overcome these solubility and stability problems. Such attempts include those described in US 5,032,392 (Varma), US 4,826,871 (Gressel et al. - I), and US 4,966,773 (Gressel et al. - II). Varma discloses aqueous ophthalmic solutions comprising retinol and/or derivatives or precursors thereof, which are solubilized in water using certain non-ionic surfactants and hydroxypropyl methylcellulose. Gressel et al. - I disclose topical ophthalmic compositions comprising low concentrations of one or more retinoids, which include near and remote analogues and functional derivatives of retinoic acid which may be biotransformed into the active form of the retinoid. Gressel et al. - II disclose topical ophthalmic compositions comprising low concentrations of microfine particles of one or more retinoids of the type disclosed in Gressel et al. - I. In the compositions of Varma and Gressel et al. - I and II, antioxidants are preferably included for purposes of stability.

SUMMARY OF THE INVENTION

It has now been surprisingly found that certain novel structural analogues of retinoids have significantly greater aqueous solubility and stability than retinoic acid and

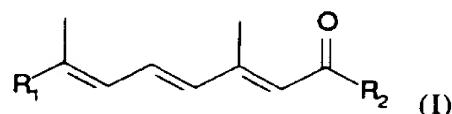
other, known retinoic acid analogues. This permits the compounds of the present invention to be formulated in standard pharmaceutical compositions and dosage forms such as solutions, semi-solids, aerosol, in lyophilized form, and including aqueous compositions.

5 It has also surprisingly been found that these soluble and stable compounds of the present invention are useful as therapeutic agents to treat a variety of diseases, such as skin disorders, and dry eye and related ailments. These compounds can be used singly or in combination.

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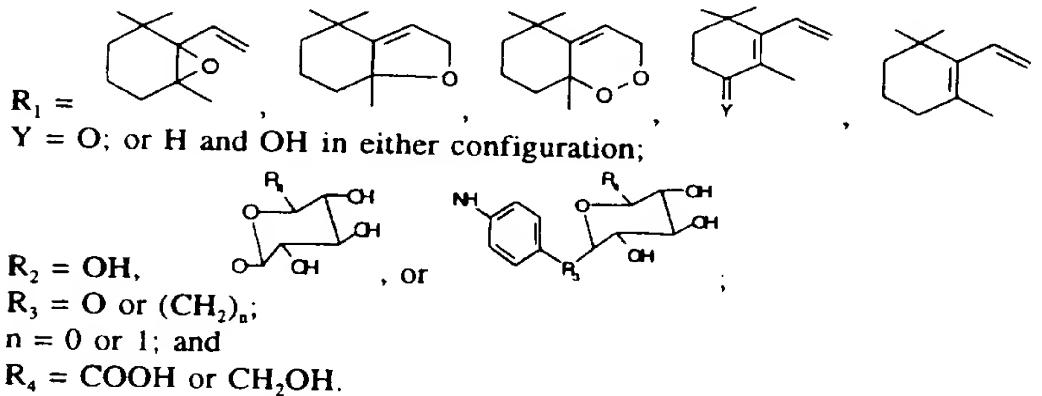
DETAILED DESCRIPTION OF THE INVENTION

The retinoic acid analogues of the present invention include the racemic and isomeric forms of the compounds of formula (I):



15

wherein:

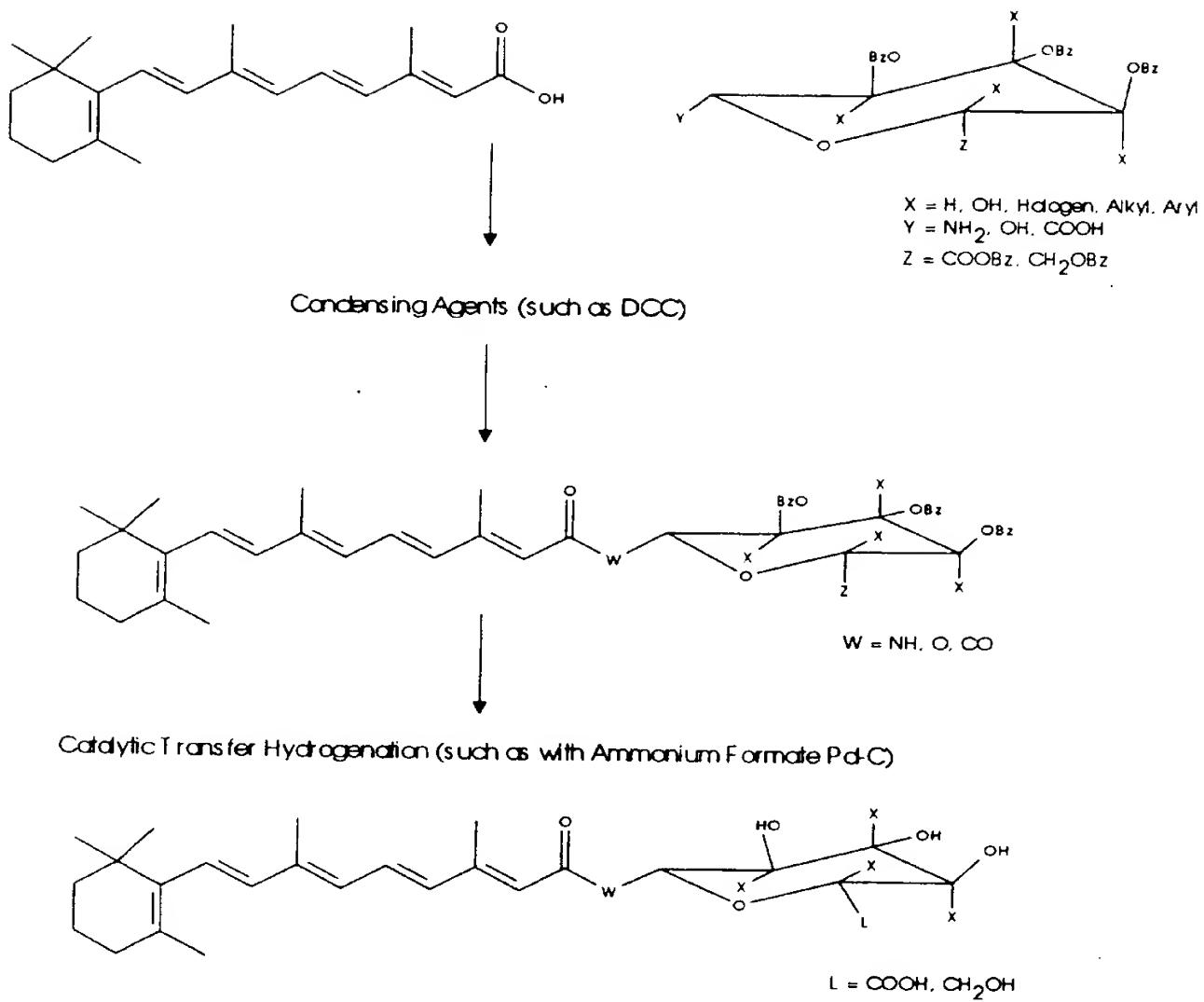


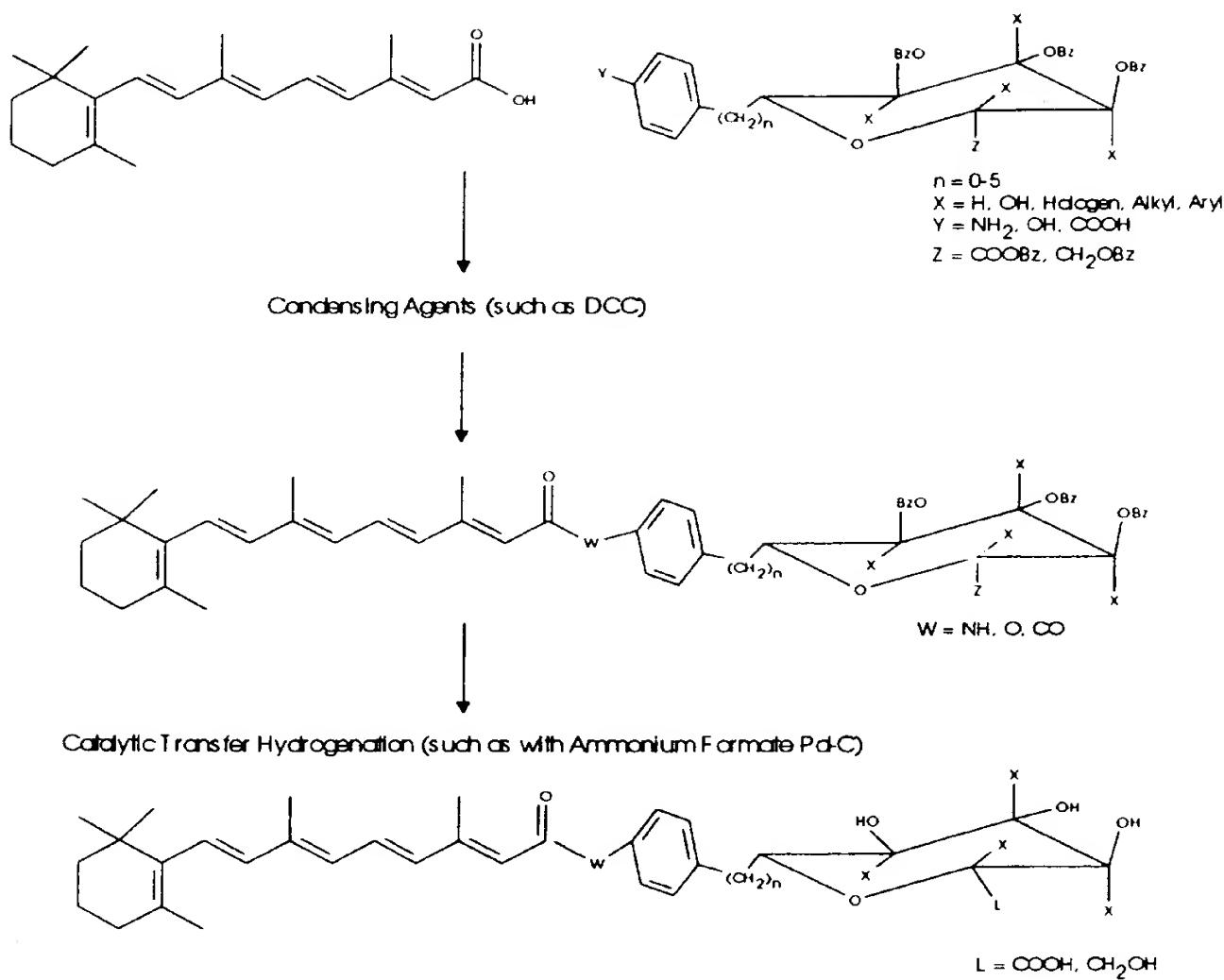
20

Such compounds are described in PCT US93/10998 (Curley). Methods for preparation of these compounds are also disclosed in the Curley application.

25 PCT US93/10998 is hereby incorporated by reference to the extent it describes the compounds of formula (I) and the methods for their preparation. For purposes of this specification, the terms "retinoids" or "retinoids of the present invention" shall refer to the compounds of formula (I) unless the context clearly indicates otherwise.

The compounds of the present invention can also be prepared by the efficient alternative synthetic route such as shown in Schemes 1 and 2, shown below. Derivatives of either benzyl-tri-*o*-benzyl- β -D-glucuronate (or glucoside) (Scheme 1) or benzyl-p-aminophenyl-tri-*o*-benzyl- β -D-glucuronate (or glucoside) (Scheme 2) and retinoic acid are reacted together in the presence of a condensing agent such as dicyclohexylcarbodiimide (DCC). This reaction is followed by catalytic transfer hydrogenation using ammonium formate palladium-on-carbon as a catalyst to yield the desired retinoid listed in Tables 1 and 2.

SCHEME 1

SCHEME 2

Preferred retinoids of the present invention include the racemic and isomeric forms of the compounds listed in the following Tables 1 and 2. Of these retinoids, those listed in Table 2 are the most preferred.

TABLE 1

A	
B	
C	
D	
E	
F	

wherein:

10 $R' = OH$;

 ; or

 ;

$R'_1 = O$ or $(CH_2)_n$;

$n = 0$ or 1 ; and

$R'_2 = COOH$ or CH_2OH .

TABLE 2

G	
H	
J	
K	
L	

10 The compositions of the present invention are primarily intended for the treatment of ocular surface disorders, particularly dry eye syndromes, inflammation, wound healing and related ailments. Symptoms include, without limitation, foreign body sensation, burning and hyperemia. For ophthalmic use, the retinoids of the present invention are formulated, either singly or in combination, at a concentration between about 0.0001 and about 2.0 percent by weight (wt%), and preferably at a concentration between about 0.01 and about 0.5 wt%. Depending on the particular compounds, it is most preferable to formulate the retinoids at a concentration of about 0.1 wt%.

15

In addition, the compositions of the present invention are intended for the treatment of skin disorders, such as acne, psoriasis and skin-wrinkling (skin-ageing), and as an aid in wound healing. For treatment of such disorders, the retinoids of the present invention are formulated, either singly or in combination, at a concentration between about 0.001 and about 2 percent by weight (wt%), preferably between about 0.01 and about 1 wt%.
5 Depending on the particular compounds, it is most preferable to formulate the retinoids at a concentration of about 0.5 wt%.

For the treatment of ocular surface disorders, a dose of one or two drops of a
10 compositions of the present invention is generally administered two to four times per day, although dosing may be more or less frequent, depending on the severity of the disease. Frequency of dosing is variably dependent upon severity; in severe cases, dosing may occur twelve to sixteen or more times per day. For dermatological use, the retinoids are usually applied topically to the affected area as needed, usually two to four times per day,
15 although administration may be more or less frequent, depending on the severity of the disease.

The ophthalmic compositions of the present invention may additionally contain sodium chloride or other suitable tonicity adjusting agents, including but not limited to:
20 potassium chloride, calcium chloride, mannitol, and glycerin. Such tonicity adjusting agents are typically used at a concentration between about 75 and about 154 mmol/L so that the resultant osmolality of the composition is between about 200 and about 350 milliOsmoles/kilogram (mOsm/kg). It is preferred that these compositions have an osmolality between about 260 and about 330 mOsm/kg. The ophthalmic compositions of
25 the present invention will generally have a pH between about 4.0 and about 9.5, preferably between about 5.0 and 8.5.

The ophthalmic compositions of the present invention may additionally contain mucomimetic polymers and lubricating agents for increased comfort and sustained duration in the eye. Examples of the above include: Dextran; cellulose derivatives, e.g.,
30 hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose; polyvinyl

5 -yrrolidone; and polyethylene glycols. In general, these polymers are present in the compositions of the present invention at a concentration between about 0.05 and about 5.0 wt%, preferably between about 0.1 and about 2.0 wt%.

10 The following Examples 1 and 2 illustrate typical compositions of the present invention.

EXAMPLE 1

15 The following are typical examples of ophthalmic compositions useful in the present invention. These compositions may be formulated in accordance with procedures known to those skilled in the art.

INGREDIENT	FORMULATION (wt%)					
	1	2	3	4	5	6
Retinoid*	0.01	0.05	0.1	0.2	0.5	0.1
NaCl	qs to 280 mOsm/kg					
NaOH and/or HCl	qs to pH**					
Dibasic sodium phosphate, anhydrous	0.1	0.1	0.1	0.1	0.1	...
Monobasic sodium phosphate, monohydrate	0.03	0.03	0.03	0.03	0.03	...
Purified Water	qs to 100%					

*Retinoid compound J, G or H selected from the group of compounds listed in Table 1.

**Physiological pH.

Preparation:

All the excipients are dissolved into an aliquot of purified water, the retinoid is then dissolved in the batch, and the pH adjusted. Purified water is then added to bring the final volume to 100%.

5

EXAMPLE 2

10 The following are additional examples of ophthalmic compositions useful in the present invention.

INGREDIENT*	FORMULATION (wt%)				
	7	8	9	10	11
Retinoid*	0.01	0.1	0.01	0.1	0.25
Hydroxypropyl methyl cellulose ("HPMC")	0.3	0.3	0.3	0.3	0.3
NaCl	qs to 280 mOsm/kg				
KCl	0.13	0.13	0.13	0.13	0.13
CaCl ₂ · 2H ₂ O	0.0053	0.0053	0.0053	0.0053	0.0053
MgCl ₂ · 6H ₂ O	0.0064	0.0064	0.0064	0.0064	0.0064
ZnCl ₂	0.00015	0.00015	0.00015	0.00015	0.00015
Sodium bicarbonate	0.1	0.3	0.3	0.1	0.1
CO ₂ and/or NaOH and/or HCl	qs to pH**				
Purified Water	qs to 100%				

*Retinoid compound J, G or H selected from the group of compounds listed in Table 2.
**Physiological pH.

Preparation:

All excipients are dissolved into an aliquot of purified water. The retinoid is then dissolved into this solution, and the pH of the solution is adjusted. Purified water is then added to bring the batch volume to 100%.

5

EXAMPLE 3

10 The following are additional examples of viscous compositions useful in the present invention:

INGREDIENT	FORMULATION (wt%)								
	13	14	15	16	17	18	19	20	21
Retinoid*	0.1	0.01	0.01	0.1	0.1	0.1	0.05	0.1	0.1
Hydroxypropyl methyl cellulose	0.5	---	0.5	0.3	0.3	0.5	1.0	0.5	---
Sodium chloride	---	---	0.41	0.41	0.41	---	0.66	0.6	0.66
Mannitol	4.5	4.5	---	---	---	4.5	---	---	---
Potassium chloride	---	---	0.13	0.13	0.13	---	0.13	0.13	0.13
Calcium chloride · 2H ₂ O	---	---	0.0053	0.0053	0.0053	0.0053	0.0053	0.0053	0.0053
Magnesium chloride - 6H ₂ O	---	---	0.0064	0.0064	0.0064	0.0064	0.0064	0.0064	0.0064
Zinc chloride	---	---	0.00015	0.00015	0.00015	0.00015	0.00015	0.00015	0.00015
Sodium bicarbonate	---	---	0.1	0.1	0.1	---	0.1	0.1	0.2
Potassium bicarbonate	---	---	---	---	---	0.1	---	---	---
Carbomer 934P	0.175	0.175	0.175	---	---	0.175	0.175	---	---
Carboxy-methyl cellulose	---	---	---	1.0	3.0	---	---	---	---
Sodium hyaluronate	---	---	---	---	---	---	---	0.1	---
Carbon dioxide and/or NaOH and/or HCl	qs to pH**	qs to pH**	qs to pH**	qs to pH**	qs to pH**	qs to pH**	qs to pH**	qs to pH**	qs to pH**
Purified Water	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%

*Retinoid compound J, G or H selected from a group of compounds listed in Table 2.

**Physiological pH.

Preparation:

Hydroxypropyl methyl cellulose, Carbomer 934P, Carboxy methyl cellulose or sodium hyaluronate is dissolved in purified water followed by the addition of other excipients. The pH of the batch is adjusted, and the retinoid is then dissolved into the solution and added to the batch.

EXAMPLE 4

10 The following are additional examples of dermatological compositions useful in the present invention:

INCIREDIENT	FORMULATION (wt%)			
	22	23	24	25
Retinoid*	0.1	0.1	0.5	0.5
Propylene glycol	5.0	5.0	5.0	5.0
Sorbitol solution, 70%	---	5.0	---	5.0
Glycerin	---	4.0	---	4.0
Polysorbate 60	0.2	---	0.2	---
Sorbic acid	0.1	---	0.1	---
Potassium sorbate	0.13	---	0.13	---
Propyl gallate	0.02	---	0.02	---
Benzyl alcohol	---	2.2	---	2.2
Emulsifying wax	10.0	12.0	10.0	12.5
Isopropyl palmitate	2.0	2.0	2.0	2.0
White wax	1.0	---	1.0	---
Stearic acid	2.5	---	2.5	---
Butylated hydroxytoluene	---	0.05	---	0.05
Citric acid or Lactic acid and/or NaOH	qs to pH**	qs to pH**	qs to pH**	qs to pH**
Purified Water	qs to 100%	qs to 100%	qs to 100%	qs to 100%

*Retinoid compound Y, G or H selected from a group of compounds in Table 2.

**Physiological pH.

Preparation:

The oil phase of the emulsion is prepared by combining and heating the lipophilic components (stearic acid, white wax, isopropyl palmitate, emulsifying wax and polysorbate 60). Propyl gallate and butylated hydroxytoluene are then dissolved in melted components. The temperature is maintained between 70° and 85° C.

The aqueous phase is prepared by the addition of the water soluble components of the formulation, and the pH is adjusted. The temperature is maintained by heating the batch to 70° - 85° C.

Preparation of emulsion: both the oil phase and aqueous phases are combined at 70° - 85° C temperature with continuous mixing. The batch is cooled to room temperature with mixing. the pH is then adjusted to the desired level using citric acid and/or NaOH. The retinoid is then separately dissolved in a portion of purified water and added to the main batch. Final batch volume is adjusted with purified water.

EXAMPLE 5

The following are additional examples of dermatological compositions useful in the present invention:

INGREDIENT	FORMULATION (wt%)			
	26	27	28	29
Retinoid*	0.1	0.1	0.5	0.5
Carbomer 941	0.6	0.3	0.6	0.3
Glycerin	5.0	7.0	5.0	7.0
Petrolatum	3.3	---	3.3	---
Mineral oil	---	6.0	---	6.0
Dimethicone	0.6	---	0.6	---
Cetyl alcohol	0.3	---	0.3	---
Stearyl alcohol	---	3.0	---	3.0
Cetearyl alcohol (and) Ceteareth-20	1.5	---	1.5	---
Glyceryl stearate (and)	---	3.0	---	3.0
PEG-100 stearate	-	-	-	-
Steareth-21	---	3.0	---	3.0
Cyclomethicone	---	4.0	---	4.0
Benzyl alcohol	2.2	1.0	2.2	1.0
Potassium sorbate	---	0.2	---	0.2
Citric acid and/or NaOH	qs to pH**	qs to pH**	qs to pH**	qs to pH**
Purified water	qs to 100%	qs to 100%	qs to 100%	qs to 100%

*Retinoid compound I, G or H selected from the group of compounds listed in Table 2.

**Physiological pH.

Preparation:

The oil phase of the emulsion is prepared by mixing together and heating the lipophilic components (such as petrolatum, mineral oil, Dimethicone, cetyl alcohol, stearyl alcohol, cetearyl alcohol (and) ceteareth-20, glyceryl stearate (and) PEG-100 stearate, steareth-21 and cyclomethicone). Propyl gallate and butylated hydroxytoluene are then dissolved in with the melted components. The temperature is maintained between 70° and 85° C.

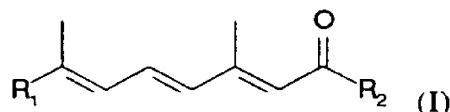
The aqueous phase is prepared by dispersing Carbomer 941 in an aliquot of purified water, followed by the addition of the water solu 10 components of the formulation and the pH adjusted. The temperature is maintained by heating the batch to 70° - 85° C.

Preparation of emulsion: both the oil phase and aqueous phases are combined at 15 70° - 85° C temperature with continuous mixing. The batch is then cooled to room temperature with mixing. The pH is then adjusted to desired level using citric acid and/or NaOH. The retinoid is separately dissolved in a portion of purified water, and then added to the main batch. Final batch volume adjusted with purified water.

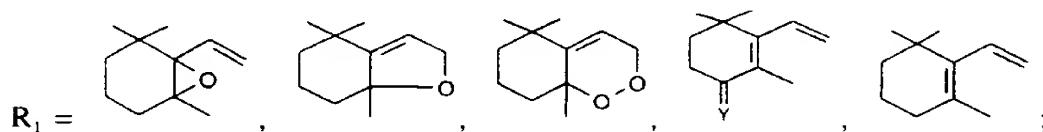
20 The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The 25 embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is Claimed is:

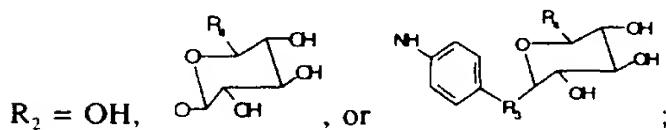
1. A topical pharmaceutical composition, comprising a pharmaceutically acceptable vehicle and a pharmaceutically effective amount of the racemic or isomeric forms of a compound of formula:



wherein:



10 $Y = O$; or H and OH in either configuration;



$R_3 = O$ or $(CH_2)_n$;

$n = 0$ or 1 ; and

$R_4 = COOH$ or CH_2OH .

15

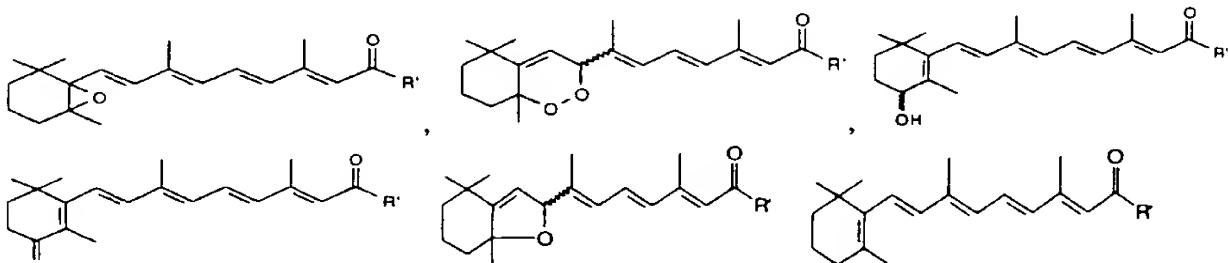
2. The topical pharmaceutical composition of claim 1, wherein the compound of formula (I) is present at a concentration between about 0.001 and about 2.0 wt%.

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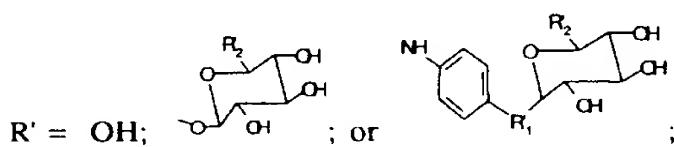
3. The topical pharmaceutical composition of claim 2, wherein the compound of formula (I) is present at a concentration between about 0.01 and about 0.5 wt%.

4. The topical pharmaceutical composition of claim 3, wherein the compound of formula (I) is present at a concentration of about 0.5 wt%.

5. The pharmaceutical composition of claim 1, wherein the compound of formula (I) is selected from the group consisting of:



5 wherein:

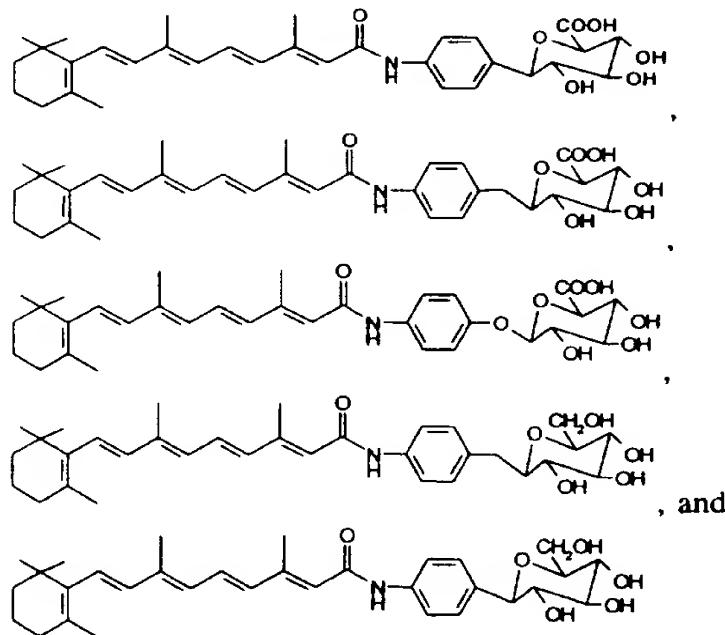


10 $R'_1 = O \text{ or } (CH_2)_n;$

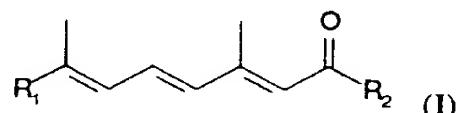
$n = 0 \text{ or } 1;$ and

$R'_2 = COOH \text{ or } CH_2OH.$

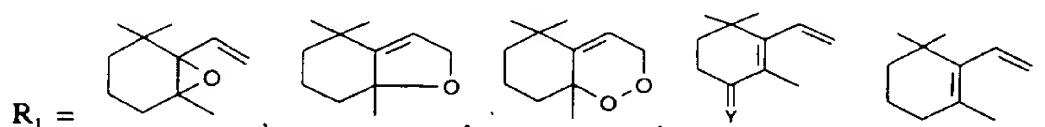
15 6. The pharmaceutical composition of claim 5, wherein the compound of formula (I) is selected from the group consisting of:



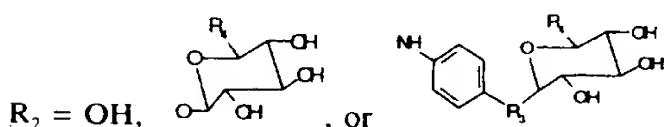
7. An ophthalmic composition comprising an ophthalmically acceptable vehicle and an ophthalmically acceptable amount of the racemic or isomeric forms of a compound of formula:



wherein:



Y = O; or H and OH in either configuration:



$\mathbf{R}_3 = \text{O}$ or $(\text{CH}_2)_n$;

$n = 0$ or 1 ; and

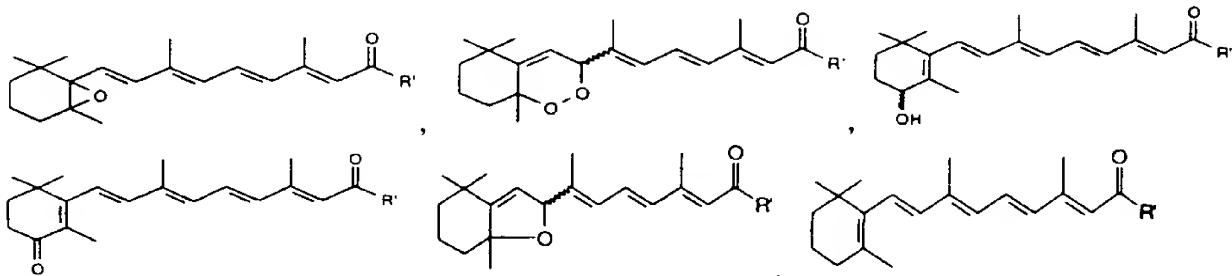
$R_4 = \text{COOH}$ or CH_3OH .

8. The ophthalmic composition of claim 7, wherein the compound of formula (I) is present at a concentration between about 0.0001 and about 2.0 wt%.

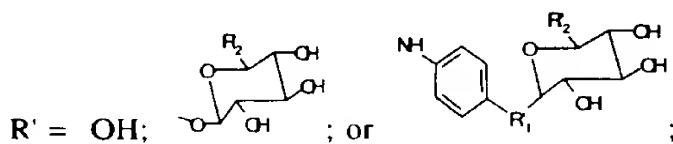
9. The ophthalmic composition of claim 8, wherein the compound of formula (I) is present at a concentration between about 0.01 and about 0.5 wt%.

10. The ophthalmic composition of claim 9, wherein the compound of formula (I) is present at a concentration of about 0.1 wt%.

11. The ophthalmic composition of claim 7, wherein the compound of formula (I) is selected from the group consisting of:



wherein:

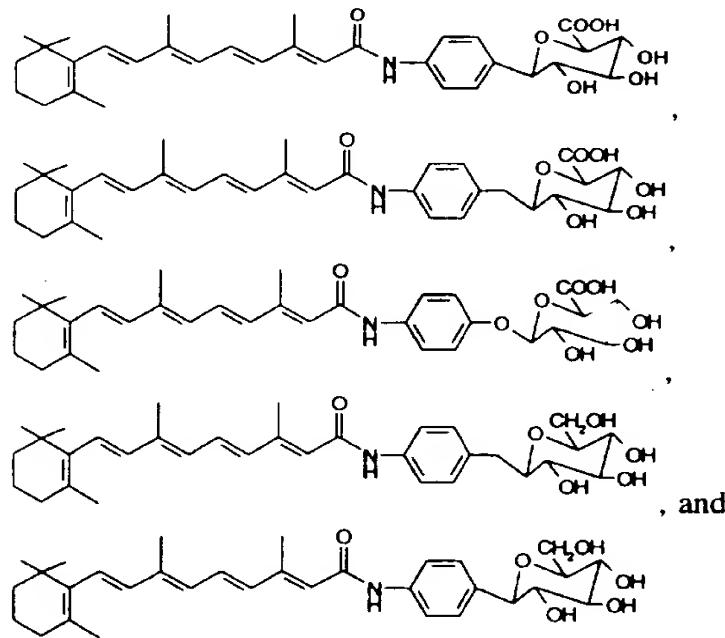


$R'_1 = O$ or $(CH_2)_n$;

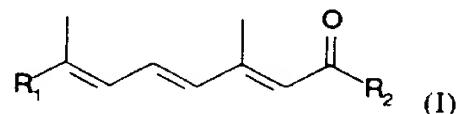
$n = 0$ or 1 ; and

$R'_2 = COOH$ or CH_2OH .

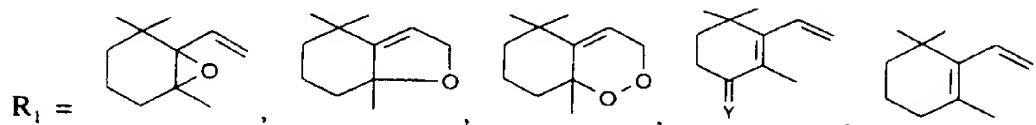
10 12. The ophthalmic composition of claim 11, wherein the compound of formula (I) is selected from the group consisting of:



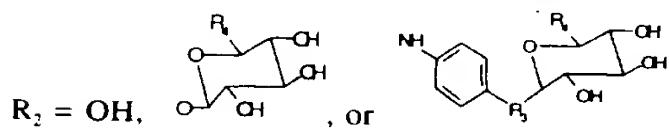
13. A method for treating ocular surface disorders, comprising topically applying to an affected eye an ophthalmically effective amount of the racemic or isomeric forms of a compound of formula:



wherein:



$Y = O$; or H and OH in either configuration;



10 $R_3 = O$ or $(CH_2)_n$;

$n = 0$ or 1 ; and

$R_4 = COOH$ or CH_2OH .

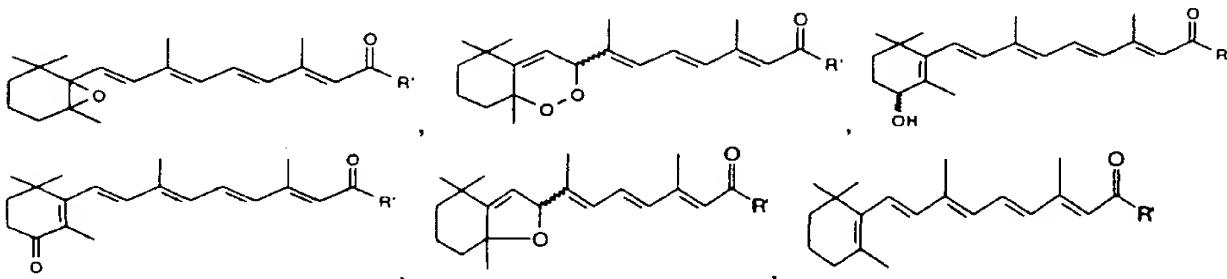
14. The method of claim 13, wherein the compound of formula (I) is present at a concentration between about 0.0001 and about 2.0 wt%.

15. The method of claim 14, wherein the compound of formula (I) is present at a concentration between about 0.01 and about 0.5 wt%.

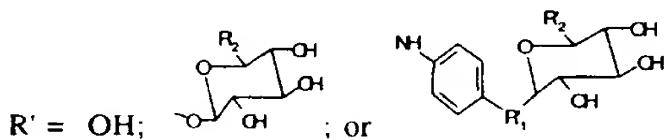
20 16. The method of claim 15, wherein the compound of formula (I) is present at a concentration of about 0.1 wt%.

17. The method of claim 13, wherein the ocular surface disorder is selected from the group consisting of dry eye syndromes.

18. The method of claim 13, wherein the compound of formula (I) is selected from the group consisting of:



5 wherein:

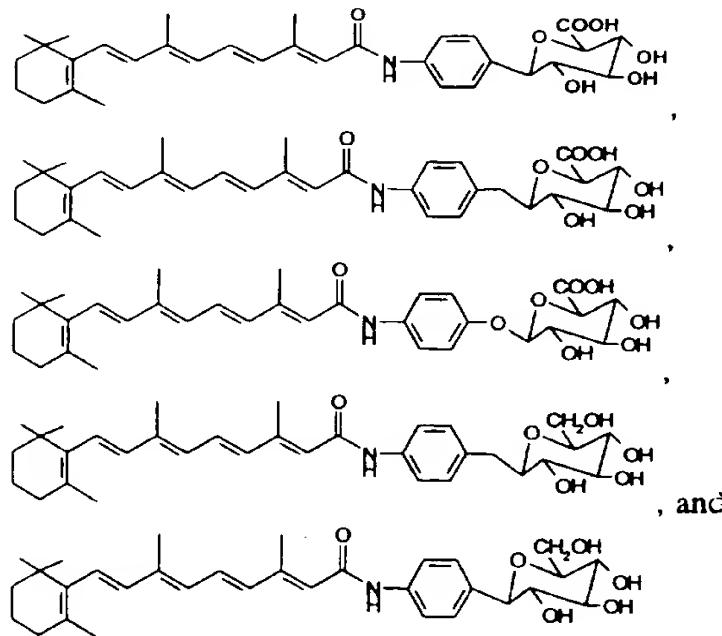


R' = OH; or

n = 0 or 1; and

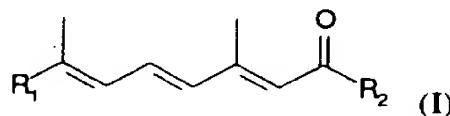
R' = COOH or CH₂OH.

10 19. The method of claim 18, wherein the compound of formula (I) is selected from the group consisting of:



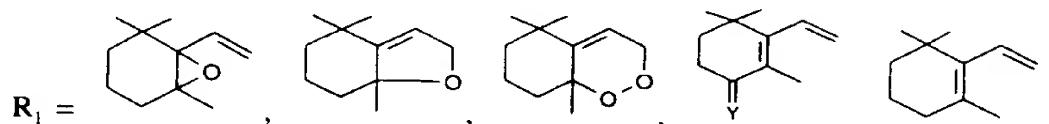
15 , and

20. A method for treating dermatological disorders, comprising topically applying to an affected area a pharmaceutically effective amount of the racemic or isomeric forms of a compound of formula:

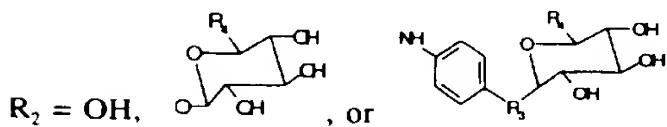


5

wherein:



$Y = O$; or H and OH in either configuration;



10

$R_3 = O$ or $(CH_2)_n$;

$n = 0$ or 1 ; and

$R_4 = COOH$ or CH_2OH .

15

21. The method of claim 20, wherein the compound of formula (I) is present at a concentration between about 0.001 and about 2.0 wt%.

22. The method of claim 21, wherein the compound of formula (I) is present at a concentration between about 0.01 and about 0.5 wt%.

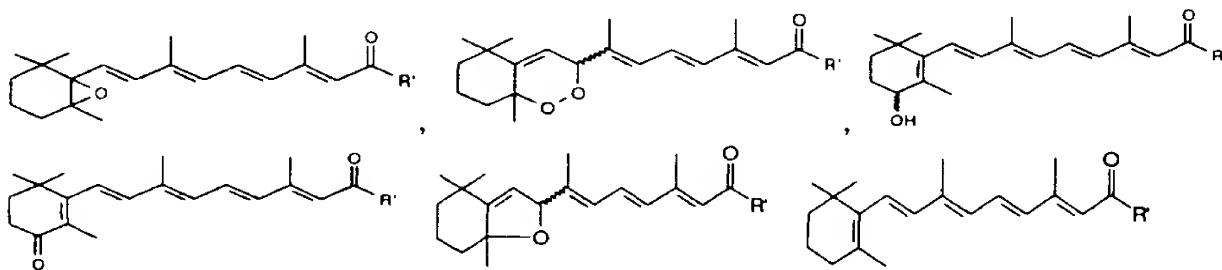
20

23. The method of claim 22, wherein the compound of formula (I) is present at a concentration of about 0.5 wt%.

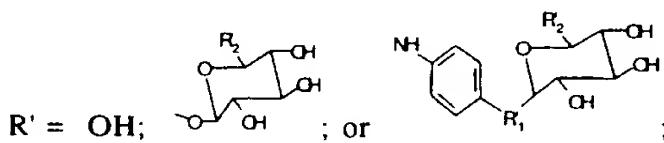
24. The method of claim 20, wherein the dermatological disorder is selected from the group consisting of: acne, psoriasis and skin-wrinkling or ageing.

25

25. The method of claim 24, wherein the compound of formula (I) is selected from the group consisting of:



5 wherein:



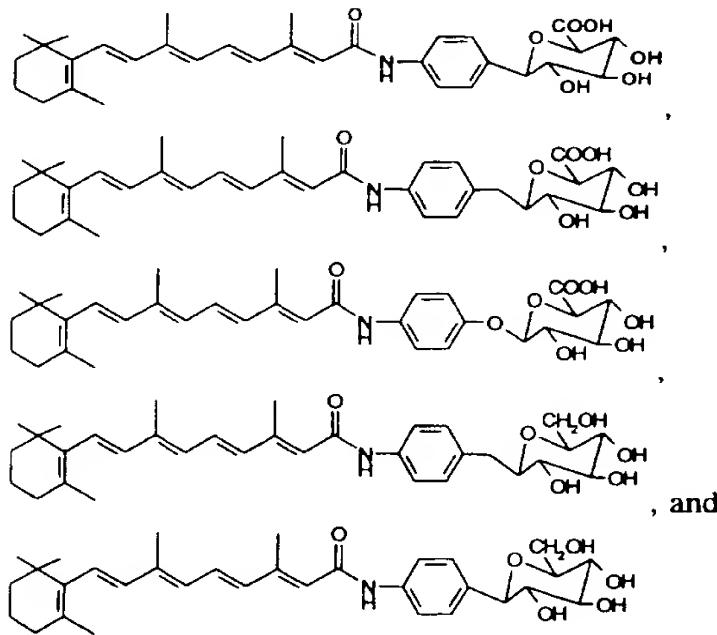
R' = OH; ; or

n = 0 or 1; and

R'2 = COOH or CH2OH.

10

26. The method of claim 25, wherein the compound of formula (I) is selected from the group consisting of:



INTERNATIONAL SEARCH REPORT

International Application No
/US 95/11314

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/20 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 966 773 (GRESSEL ET AL.) 30 October 1990 see claims; examples	1-5, 7-11, 13-18, 20-23
X	US,A,5 037 655 (GIOVANONI) 6 August 1991 see claims	1-5, 7-11, 13-16,18
X	EP,A,0 472 225 (MOËT-HENNESSY) 26 February 1992 see the whole document	1-5, 20-24
X	FR,A,2 666 015 (L' OREAL) 28 February 1992 see the whole document	1-5, 20-24
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- 'O' document referring to an oral disclosure, use, exhibition or other means
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- '&' document member of the same patent family

Date of the actual completion of the international search

23 January 1996

Date of mailing of the international search report

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Klaver, T

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/11314

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 11030 (OHIO STATE UNIVERSITY) 26 May 1994 cited in the application see claims ---	1-6
P,Y	WO,A,95 09862 (CIBA-GEIGY) 13 April 1995 see the whole document ---	1-6
A	J. CARBOHYDR. CHEM., vol. 13, no. 2, 1994 pages 303-312, M.J. PANIGOT ET AL. 'Preparation of 4-retinamidophenyl- and 4-retinamidobenzyl- α -glycosyl and α -glucuronosyl analogs of the glucuronide of 4-hydroxyphenylretinamide as potential stable cancer chemopreventive agents.' ---	
A	MED. CHEM. LETT., vol. 4, no. 17, 1994 pages 2117-2122, M.J. ROBARGE ET AL. 'N-linked analogs of retinoid O-glucuronides: potential cancer chemopreventive/chemotherapeutic agents.' -----	

INTERNATIONAL SEARCH REPORT

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International Application No

PCT/US 95/11314

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		DE-A-	3686325	10-09-92
		EP-A, B	0229561	22-07-87
		JP-B-	5015689	02-03-93
		JP-A-	62215513	22-09-87
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FR-A-2666015	28-02-92	NONE		
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WO-A-9509862	13-04-95	GB-A-	2282596	12-04-95
		AU-B-	7809694	01-05-95